Memory Enhancement Induced by Hypothalamic/ Fornix Deep Brain Stimulation

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Bilateral hypothalamic deep brain stimulation was performed to treat a patient with morbid obesity. We observed, quite unexpectedly, that stimulation evoked detailed autobiographical memories. Associative memory tasks conducted in a double-blinded "on" versus "off" manner demonstrated that stimulation increased recollection but not familiarity-based recognition, indicating a functional engagement of the hippocampus. Electroencephalographic source localization showed that hypothalamic deep brain stimulation drove activity in mesial temporal lobe structures. This shows that hypothalamic stimulation in this patient modulates limbic activity and improves certain memory functions.

Ann Neurol 2008;63:119–123

Approximately 30,000 patients have received deep brain stimulation (DBS) surgery to treat Parkinson's disease and other movement disorders. With the safety and efficacy of DBS surgery now being widely accepted, novel brain targets and indications for DBS are being considered. The hypothalamus is one of such targets.

In animal models, stimulation in hypothalamic areas influences feeding behavior[1–3] and modulates memory function.[4] In humans, hypothalamic DBS recently has been used to treat cluster headache and even aggressiveness.[5,6] We used hypothalamic DBS in an investigational study to treat a patient with morbid obesity and observed, quite unexpectedly, that stimulation spontaneously evoked detailed autobiographical memory events. This striking phenomenon led us to investigate the anatomic substrates and mechanism through which hypothalamic stimulation could drive this type of memory.

Subject and Methods

Case History

A 50-year-old man with a life-long history of obesity (190.5kg; body mass index, 55.1kg/m^2) did not respond to multiple treatments, including dietary regimens, psychological interventions, group therapies, and medications. Medical comorbidities included type II diabetes, hypertension, and obstructive sleep apnea. He refused gastric bypass and bariatric surgery believing that he would continue to eat excessively despite these interventions. Given his resistance to treatment, the concern with the long-term health consequences of morbid obesity, and our group's long-standing interest in functional neurosurgery and DBS, he was referred to consider the possibility of a neurosurgical treatment.

Hypothalamic lesion surgery had been used previously to treat obesity,[7,8] but we believed that the safety and reversibility of DBS offered a significant advantage. The possibility of hypothalamic stimulation for appetite control was therefore considered. After extensive discussions, which emphasized the uncertainty of benefits and the potential for adverse effects, the patient asked to proceed with surgery. The procedure was approved by the University Health Network Research Ethics Board, and written informed consent was obtained under the guidance of a hospital ethicist, who served as a consent monitor. The basis of the approval for this man was the refractory nature of the obesity, the exhaustion of reasonable therapeutic alternatives, and the possibility of reducing the health risks of chronic obesity should the intervention prove successful. Hypothalamic stimulation was proposed based on experimental studies of appetite control in rodents, dogs, and nonhuman primates,[1–3] and the experience, albeit limited, of hypothalamotomy for obesity in humans.[7,8]

Surgery and Intraoperative Observations

A stereotactic frame was applied to the patient's head and a computed tomographic scan was obtained (because of his weight, the patient could not undergo magnetic resonance imaging). DBS electrodes (Medtronic model 3387; Medtronic, Minneapolis, MN) were implanted bilaterally in the ventral hypothalamus with the patient receiving local anesthesia without sedation. To identify potential sites to suppress appetite, we tested the effects of stimulation at each of the four contacts of these electrodes in the operating room. Contacts were numbered from 0 to 3 (right side) and 4 to 7 (left side), with 0 and 4 being the most ventral contacts (deepest) and 3 and 7 the most dorsal ones. Unexpectedly, the patient reported sudden sensations that he described as "déjà vu" with stimulation of the first contact tested (contact 4: 3.0 volts, 60-microsecond pulse width [pw], and 130Hz). He reported the sudden perception of being in a park with friends, a familiar scene to him. He felt he was younger, around 20 years old. He recognized his epoch-appropriate girlfriend among the people.

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Received July 5, 2007, and in revised form Aug 31. Accepted for publication Oct 4, 2007.

This article includes supplementary materials available via the Internet at http://www.interscience.wiley.com/jpages/0364-5134/suppmat

Published online Mon 00, 2008, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21295

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He did not see himself in the scene, but instead was an observer. The scene was in color; people were wearing identifiable clothes and were talking, but he could not decipher what they were saying. As the stimulation intensity was increased from 3.0 to 5.0 volts, he reported that the details in the scene became more vivid. The same perceptions were obtained during blinded, sequential successive stimulation of individual contacts 0, 1, 4 and 5, using monopolar stimulation (60-microsecond pw, 130Hz). All experiential perceptions were time-locked with stimulation, were specific to the electrode contact and stimulation parameters used, and were obtained at a reproducible current threshold with stimulation performed in a double-blinded manner. At certain contacts, at intensities of 5 volts or greater, he experienced stimulation dose-dependent adverse effects, including feeling an unpleasant generalized warming sensation that was followed by facial hyperemia and sweating. There were no overt associated changes in the monitored vital signs (blood pressure, heart rate, and electrocardiogram). In addition, when stimulation was rapidly increased from 0 to 5 volts at the most ventral contacts, in closest proximity to the optic tracts, the patient transiently saw flashes of light in the contralateral visual field consistent with current spread to the ipsilateral optic tract. There were no reproducible changes in his subjective sensation of hunger with stimulation on a self-rated 1 to 10 scale with these settings. Once stimulation at each contact was tested, the electrodes were secured to the skull and the procedure was completed.

A dual-channel pulse generator (Kinetra; Medtronic) was implanted with the patient under general anesthesia. The postoperative course was complicated by a generalized seizure on the evening of the procedure and aspiration pneumonia. The patient was not receiving electrical stimulation, and no obvious cause for the seizure was identified with brain imaging. The stimulators were left "off" during his hospitalization and convalescence.

The position of the electrodes was confirmed with computed tomography imaging (see Supplementary Fig 1A). The images acquired were reconstructed on a surgical navigation workstation (Stealth Station; Medtronic), and the coordinates of the distal contacts were plotted onto Schaltenbrand and Wahren stereotactic space.[9] The coordinates of the tip of the right electrodes were 6.0mm lateral, 10.5mm anterior, and 11.7mm below the midcommissural point. The tip of the left electrode was 4.2mm lateral, 11.0mm anterior, and 11.3mm below midcommissural point. Contacts that most readily induced déjà vu experiences with stimulation were located in the hypothalamus and *estimated* to be in close association to the fornix (see Supplementary Figs 1B, C), a major fiber pathway that interconnects the subiculum and hippocampus to the mamillary nuclei and septal area.[10]

Neuropsychological/Memory Evaluation

Comprehensive neuropsychological assessment with standardized tests was conducted at baseline and after 3 weeks of

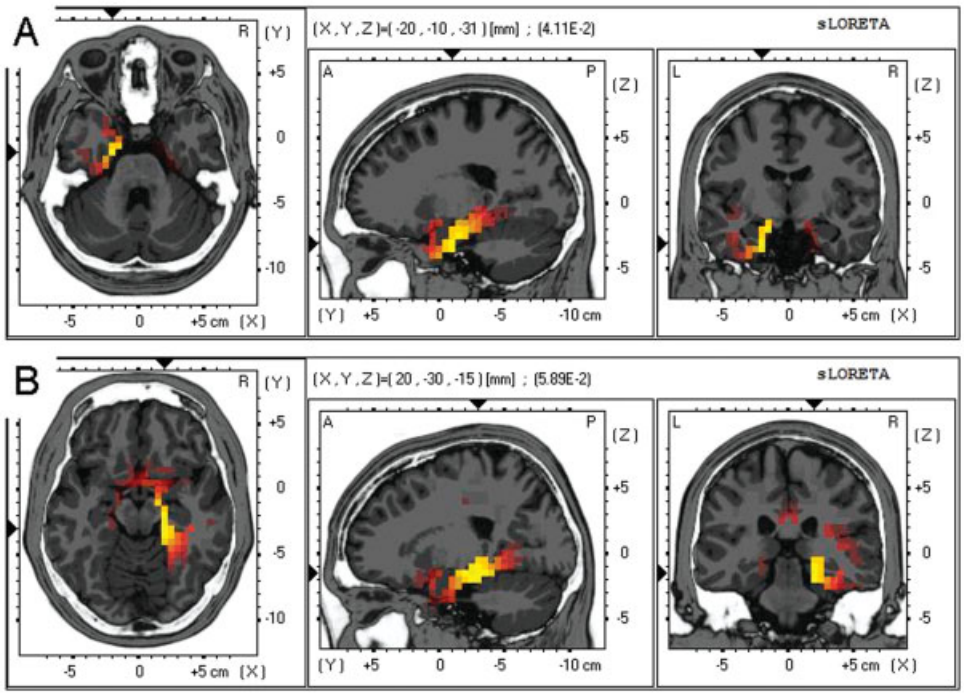

Fig. Hypothalamic stimulation drives medial temporal lobe structures. Standardized low-resolution electromagnetic tomography (sLORETA) was used to map the brain areas affected by right (A) or left (B) hypothalamic stimulation. Data were mapped onto axial (left), sagittal (center), and coronal (right) magnetic resonance brain images. Significant current density changes with stimulation are shown using a linear color scale with yellow representing maximal current density values. Stimulation led to localized changes in the activity of ipsilateral mesial temporal lobe structures, mainly the hippocampal formation and the parahippocampal gyrus region.

hypothalamic stimulation (Table 1). To ascertain whether differences in the patient's scores on two test occasions exceeded practice effects, we used the reliable change index (raw data provided in the supplementary materials).

The effects of stimulation on memory were further characterized using recognition tasks with high sensitivity and specificity for hippocampus-dependent retrieval processes. Each task was performed twice, with the stimulator "on" or "off" in a double-blinded fashion. Task 1 was conducted over 2 days, 1 week apart, with the "off" condition randomly assigned to be completed first. In the study phase, a series of 80 word pairs (eg, plane-turtle, boy-car) was presented and the patient was to decide which of the words was more pleasant. Ten minutes later, he underwent recognition testing, having to ascertain whether test pairs were *intact* (same pair as studied; eg, plane-turtle, boy-car), *recombined* (words from different studied pairs; eg, plane-car), or *new* (one or both words never seen before; eg, apple-chair). For items recognized as *intact* or *recombined,* the patient was then asked to make a *remember* or *know* decision. *Remember* was to be reported when he could recall elements of the study episode (eg, what he thought when comparing the words on *intact* pairs, or the true alternative for pairs described as *recombined*). In contrast, *know* was to be reported when the pair was familiar, but he was unable to recall the original context of the association between the words.

A second recognition task (task 2)[11] with a different design was administered after 12 months of stimulation. In this case, the "on" and "off" stimulation conditions were tested on a single day, with a 1-hour intertest interval. Once again, the "off" condition was randomly assigned to be completed first. During this study phase, 120 word pairs were presented and the patient was instructed to generate aloud a meaningful sentence that contained the 2 words. Two different instructions were then administered.[11] For the first half of the studied pairs (word recognition), the patient was to identify all pairs that contained two studied words, in which case *intact* and *recombined* pairs would comprise positive responses. For the second half of the studied pairs (associative recognition), he was asked to identify only studied pairs (ie, *intact* but not *recombined*). In this case, a positive response to *recombined* items would be based on familiarity in the absence of recollection of the original context. The proportion of responses to *recombined* pairs in these two task conditions was used to obtain estimates of recollection and familiarity (Table 2).

Standardized Low-Resolution Electromagnetic Tomography

Because the patient's weight precluded positron emission tomography or magnetic resonance imaging, electroencephalographic source localization (standardized low-resolution electromagnetic tomography [sLORETA])[12] was conducted 1 month after stimulation onset to determine the brain regions activated with hypothalamic stimulation (see supplementary materials for details).

For sLORETA, bipolar stimulation of the hypothalamus was conducted at 3Hz with each electrode being investigated

Table 1. **Neuropsychological Testing at Baseline before Surgery and after Chronic Hypothalamic Stimulation**

Test	Baseline	Postoperative
WAIS Full-Scale Intelligence Quotient[a]	125	134
WAIS Attention Index[a]	108	119[b]
Trail Making Test of processing speed (average Parts A and B)[c]	60	50
Verbal Fluency (average phonemic and semantic)[c]	43	50
California Verbal Learning Test (total learning)[c]	40	77[b]
California Verbal Learning Test (short-delay recall)[c]	40	70[b]
California Verbal Learning Test (long-delay recall)[c]	55	70[b]
Spatial Associative Learning (trials to criterion)[c]	39	54[d]
Wechsler Memory Scale-III Face Recognition (Immediate)[c]	62	58
Wechsler Memory Scale-III Face Recognition (Delay)[c]	68	63
Behavioral Evaluation of Memory Figural Learning[c]	77	81
Behavioral Evaluation of Memory Figural Recall[c]	79	79
Beck Depression Inventory (raw scores)	29	27
Spielberger State Anxiety[c]	76	79

Postoperative scores were obtained after 3 weeks of continuous stimulation (bilateral stimulation, 2.8 volts, 130Hz, 60-microsecond pulse width, contacts 0 and 4 as cathodes, case as anode). Stimulation was initiated at the first postoperative office visit. The settings chosen did not produce any acute overt memory, behavioral, sensory, or autonomic effects.
[a]Scaled scores: mean = 100; standard deviation (SD) = 15.
[c]T scores: mean = 50; SD = 10.
[b]Measures in which pre-post change exceeds the 95% confidence interval for reliable change.
[d]Measures showed performance increase of greater than 1.5 SD units; normative test-retest data for reliable change computation are not available. WAIS = Wechsler Adult Intelligence Scale.

Table 2. **Hypothalamic Stimulation Increases Recollection**

Condition	Task 1		Task 2	
	Recollection Index[a,b]	Familiarity Index[c]	Recollection Index[b,d]	Familiarity Index[e]
Stimulation "off"	0.17	0.45	0.13	0.57
Stimulation "on"	0.38	0.28	0.38	0.47
95% CI[f]	0.11	0.25	0.18	0.37

Results of associative recognition tasks with the patient tested in a double-blinded manner with the stimulation randomly assigned to being "on" or "off."
[a]Proportion of correct *remember* responses in the *remember/know* task. Mean and standard deviation (SD) from 10 healthy control subjects tested in a concurrent study = 0.22 ± 0.10 (unpublished data).
[b]Measures in which the magnitude of test-retest change exceeded the 95% confidence interval (CI) for reliable change based on control data.
[c]Familiarity estimate for the remember/know task based on assumption of independent recollection and familiarity processes (ie, Yonelinas and Jacoby's[13] Independence Remember/Know procedure); Familiarity = [Know/(1 − Remember)]. Mean and SD from 10 healthy control subjects tested in a concurrent study = 0.24 ± 0.14 (unpublished data). Note that false-positive rates are similar for the patient on the two sessions ("off" = 0.11; "on" = 0.14) and control subjects (mean = 0.10 ± 0.05).
[d]Proportion of correctly recognized *recombined* word pairs when task required positive response to both intact and recombined pairs − falsely recognized *recombined* pairs when asked to identify only intact pairs. Mean and SD from 24 healthy control subjects tested in a concurrent study = 0.48 ± 0.17.[11]
[e]Proportion of falsely recognized *recombined* word pairs/[1 − Recollection Index]. Mean and SD from 24 healthy control subjects tested in a concurrent study = 0.31 ± 0.18.[11]
[f]Change required to exceed 95% CI on normative test-retest sample.

independently (130Hz was not used because of associated high-frequency electrographic artifacts that preclude analysis with sLORETA). The intensities applied varied between 1 and 10 volts, and the pws between 90 and 450 microseconds. Five hundred consecutive stimuli were time-locked, and the evoked responses were averaged and compared with baseline electroencephalographic activity. sLORETA presents blurred images of statistically standardized current density distributions on a cortical grid of 6,239 voxels with accurate localization.[12]

Results

This report emphasizes the effects of hypothalamic stimulation on memory function. The outcome with respect to appetite and obesity is available in the supplementary materials.

The effects of stimulation at each contact were examined at the first office visit, 2 months after hospital discharge. On turning on the electrical stimulation, we induced autobiographical memory effects that were similar to those previously observed in the operating room. These findings were captured on videotape (see video in the supplementary materials). Experiential sensations were elicited with stimulation of either the right or left electrodes, with the lowest threshold for inducing these perceptions (3.0 volts, 130Hz, 60-microsecond pw) being recorded at the most ventral contacts. The nature and content of the memories induced by stimulation were similar despite changing from right to left sides and were independent of the contact or stimulation parameters being used. As the stimulation intensity was increased from 3.0 to 5.0 and 7.0 volts, the patient reported greater details in the scene and related that the memory became richer and more vivid. With high intensities of stimulation (≥7.0 volts) at certain contacts, additional phenomena were observed including the perception of phosphenes in the contralateral visual field, facial hyperemia, and sweating. Chronic stimulation was applied at a setting that was free of any overt memory, behavioral, sensory, or autonomic effects (bilateral stimulation: 2.8 volts, 130Hz, 60-microsecond pw, contacts 0 and 4 as cathodes, case as anode).

Neuropsychological Assessment

The results of neuropsychological testing are shown in Table 1. Before surgery, the patient scored in the average to high average range in all cognitive domains. After 3 weeks of continuous hypothalamic stimulation, there were significant improvements on the California Verbal Learning Test (above the 95% confidence interval for reliable change index) and Spatial Associative Learning Test (>1.5 standard deviation units). Other neuropsychological measures were largely unaffected, with both increases and decreases seen on a few tests of processing speed and attention (see supplementary materials for raw data on reliable change calculations). The lack of global improvements across the various tests speaks against a nonspecific enhancement in memory as a consequence of practice, learning, or increased attention or motivation with stimulation.

Does Hypothalamic Stimulation Drive Hippocampus-Mediated Memory Function?

The patient was much more likely to provide a *remember* response to recognized stimulus pairs in the "on" stimulation (70%) than the "off" stimulation (43%) condition. The procedure that Yonelinas and Jacoby[13] proposed was used to obtain purer estimates of recollection and famil-

iarity processes, and this demonstrated that the former was markedly increased with stimulation (see Table 2).[13] Similar estimates of these processes in task 2 replicate a striking increase in the recollection index despite alternate test versions using different word lists, recognition tasks, and estimation methods (see Table 2). In contrast, stimulation did not have a significant effect on familiarity estimates in either experimental task. As shown in Table 2, the improvement in recollection with stimulation in both tasks was beyond that expected with repeated testing in a sample of healthy control subjects.

The observation that memory improvement with hypothalamic stimulation was largely restricted to enhanced recollection and not to familiarity-based recognition speaks to the specificity of the effect. Considering the entire body of data from both experimental and clinical tasks, it is unlikely that global changes in attention, motivation, or affect were the primary effects of stimulation-induced enhancement in these memory processes.

Does Hypothalamic Stimulation Drive the Activity in the Medial Temporal Lobe?

To assess whether hypothalamic stimulation was driving hippocampal activity, we examined the brain regions activated with stimulation with sLORETA.[12] Unilateral hypothalamic DBS through either the right or left electrodes led to a significant increase in the activity in ipsilateral mesial temporal lobe structures, mainly the hippocampus and parahippocampal gyrus region (Fig).

Discussion

This study shows that electrical stimulation of the hypothalamus modulates limbic activity and improves hippocampus-dependent memory function. Acute hypothalamic stimulation induced experiential perceptions that were similar to those reported in epileptic patients receiving stimulation through electrodes implanted in the hippocampus/amygdala or over the temporal cortex.[14,15] In addition, sLORETA showed that the medial aspects of the temporal lobe, mainly the hippocampus and parahippocampal gyrus, were activated during hypothalamic stimulation. Performance improved on measures of recollection that strongly correlate with hippocampal activation.[16–18]

Electrical stimulation in this high-density area could be affecting a number of neural elements. We cannot be sure how much of the effect is related to stimulation of nuclei versus axons coursing in the hypothalamus. At this time, we believe that the results are consistent with driving the activity of the hippocampal memory circuit through stimulation of the fornix. The effects of hypothalamic stimulation on memory shown here represent an unanticipated collateral effect in the context of a putative treatment for morbid obesity. Nevertheless, just as DBS can influence motor[19] and limbic circuits,[20] it may be possible to apply electrical stimulation to modulate memory function and, in so doing, gain a better understanding of the neural substrates of memory.

We thank Drs. J. Dostrovsky and W. Hutchinson for their ongoing neurophysiological expertise. Andres M. Lozano is a Canada Research Chair in Neuroscience.

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